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PcT/EP03/3661

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Signed Stephen Hordley

Dated 11 March 2003

PCT/EP 03/03661

Patents Form 1/77

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1/77

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P01/7700 0.00-0208045.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

- 8 APR 2002

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — DES/HG/P33027

2. Patent application number
(The Patent Office will fill in his part) — 0208045.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

473587003.

United Kingdom

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

8072555006.

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

PCT/EP03/03661

Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	17
Claim(s)	
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature S C Hockley Date 5-Apr-02

12. Name and daytime telephone number of person to contact in the United Kingdom: S C Hockley 01279 644355

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
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COMPOUNDS

This invention relates to cyclopentene compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of prostaglandin mediated diseases.

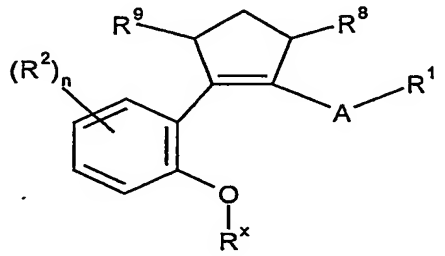
The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4). The EP_1 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP_1 receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* S Narumiya et al, Physiological Reviews 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology* (1994, 112, 735- 740) suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation* (2001, 107 (3), 325) shows that in the EP_1 knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP_1 receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDS and/or COX-2 inhibitors.

In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE_2-induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor.

WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

Accordingly the present invention provides compounds of formula (I);



(I)

wherein;

A represents an optionally substituted phenyl, or a 5- or 6- membered heterocyclyl group;

R^1 represents CO_2R^4, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted (C_{1-6})alkyl, optionally substituted (C_{1-6})alkenyl, $-SO_2(C_{1-6})$alkyl, $-SO_2NR^5R^6$, $-NR^5CONR^5R^6$, tetrazolyl or $COSO_2NR^5R^6$;

R^2 independently represents halo, optionally substituted (C_{1-6})alkyl, CN, SO_2R^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted (C_{1-8})alkyl or $-CH_2$-phenyl;

R^4 represents H or an optionally substituted (C_{1-6})alkyl;

R^5 represents H or an optionally substituted (C_{1-6})alkyl;

R^6 represents H or an optionally substituted (C_{1-6})alkyl, optionally substituted $-SO_2$aryl, optionally substituted $-SO_2$heterocyclyl group, CN or COR^7;

R^7 represents H or an optionally substituted aryl;

R^8 and R^9 independently represent H or (C_{1-6})alkyl;

n is an integer from 0 to 2;

m is an integer from 0 to 2;

wherein R^1 is attached to the group A in the 3 position relative to the bond attaching A to the cyclopentene ring;

or pharmaceutically acceptable derivatives thereof.

Preferably A is selected from an optionally substituted phenyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl; more preferably A is an optionally substituted phenyl.

Preferably R^1 represents CO_2R^4.

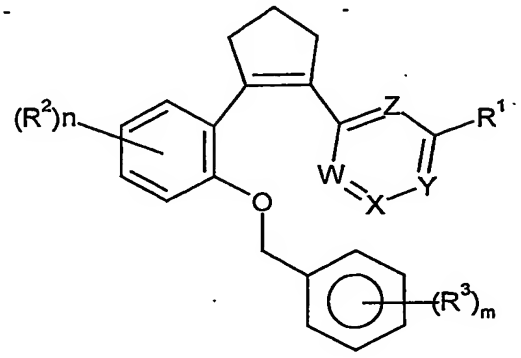
Preferably R^2 represents halogen, optionally substituted (C_{1-6})alkyl, CN or $-SO_2(C_{1-6})$alkyl.

Preferably R^8 represents methyl or H.

Preferably R^9 represents H.

Preferably when R^x represents an optionally substituted (C_{1-8})alkyl, the alkyl group is preferably $CH_2(C_{5-6})$cycloalkyl.

Preferred compounds of formula (I) are compounds of formula (II);



(II)

wherein

R^1 is CO_2R^4;

R^2 is halogen, optionally substituted (C_{1-6})alkyl, CN or $SO_2(C_{1-6})$alkyl;

R^3 independently represents halo or an optionally substituted $O(C_{1-6})$alkyl, or (C_{1-6})alkyl;

m is an integer from 0 to 2;

n is an integer from 0 to 2;

W, X, Y and Z represents CH or N wherein at least one of W, X, Y or Z is CH;

or pharmaceutically acceptable derivatives thereof.

Preferably R^3 represents halo or optionally substituted $O(C_{1-6})$alkyl more preferably halo or OMe.

Preferred compounds are selected from;

3-[2-(2-Benzyloxy-5-chloro-phenyl)-cyclopent-1-enyl]-benzoic acid; or

3-[2-(2-Benzyloxy-phenyl)-cyclopent-1-enyl]-benzoic acid;

and pharmaceutically acceptable derivatives thereof.

Preferably compounds are selective for EP_1 over EP_3. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP_1 over EP_3.

The invention is described using the following definitions unless otherwise indicated.

The term 'pharmaceutically acceptable derivative' means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the physiological acceptable salts thereof. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse , J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms 'halogen or halo' are used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof.

The term 'alkoxy' as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group.

The term 'haloalkyl' means an alkyl group, including straight, branched or cyclic structures, of the indicated number of carbon atoms in which one or more hydrogen atoms have been replaced by halogen

atoms, with up to complete substitution of all hydrogen atoms with halo groups. (C_{1-6})haloalkyl, for example, includes $-CF_3$, $-CF_2CF_3$ and the like.

The term 'haloalkoxy' means an alkoxy group, including straight, branched or cyclic structures, of the indicated number of carbon atoms in which one or more hydrogen atoms have been replaced by halogen atoms, with up to complete substitution of all hydrogen atoms with halo groups. (C_{1-6})haloalkoxy, for example, includes $-OCF_3$, $-OCF_2CF_3$ and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond. (C_{2-6})alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term 'heterocyclyl' as a group or as part of a group means a non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents. Examples of 5- membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyrizinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

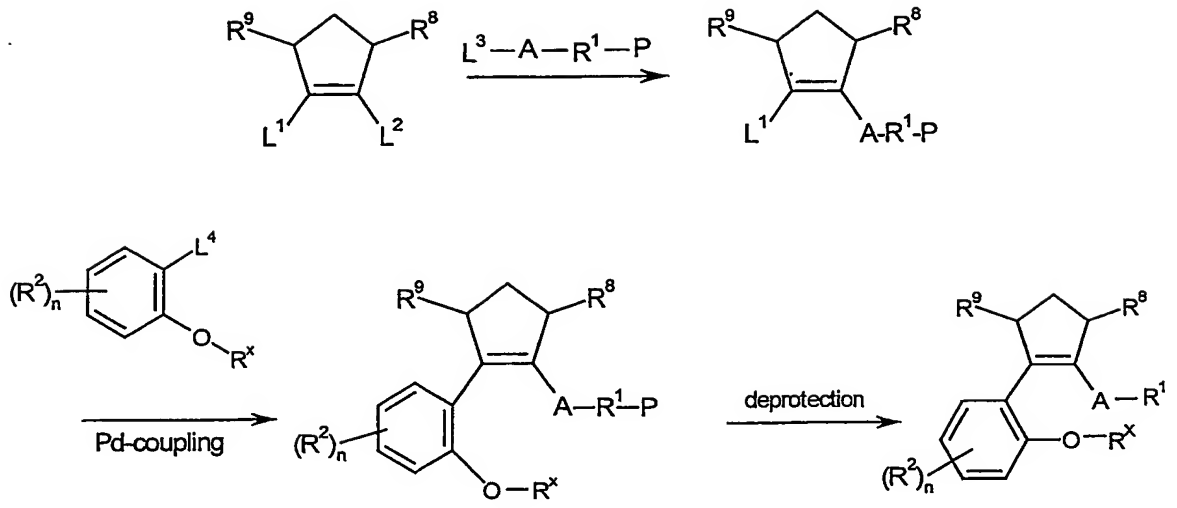
The term 'aryl' means a 5- or 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

The term 'heteroaryl' as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. Examples of "heteroaryl" used herein include furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole.

Optional substituents for alkyl or alkenyl groups are OH, CO_2R^4, NR^4R^5, (O),-O(C_{1-6})alkyl or halo, wherein R^4, R^5 and R^6 are as herein before defined.

Optional substituents for A, aryl, heteroaryl or heterocyclyl groups are C_{1-6}alkyl, C_{1-6}alkoxy and halogen.

Compounds of formula (I) can be prepared as set forth in the following scheme.



wherein L^1, L^2, are leaving groups for example halo, or triflate; L^3 and L^4 is an activating group for example selected from stannanes including trialkystannane, and boranes including boronic acid and boronate; P is a protecting group for example methyl or ethyl esters; and A, R^8, R^9 and R^x are as defined for compounds of formula (I). L^1 can be converted to $L^{1'}$, wherein $L^{1'}$ is an activating group for example a stannane or borane, and in this situation L^4 can be halo or triflate.

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention bind to the EP_1 receptor and are therefore useful in treating EP_1 receptor mediated diseases.

In view of their ability to bind to the EP_1 receptor, the compounds of the invention may be useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) may be useful as analgesics. For example they may be useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also useful in the treatment of bone disease characterised by abnormal bone metabolism or resorbtion such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) are also useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also useful in the treatment of neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also useful in the treatment of tinnitus.

The compounds of formula (I) are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP_1 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

EXAMPLE 1: 3-[2-(2-Benzyloxy-5-chloro-phenyl)-cyclopent-1-enyl]-benzoic acid

a) Intermediate I: 4-Chloro-2-iodophenol (Tetrahedron, 1995, **51**, 8555)

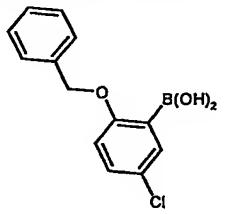
2-Amino-4-chlorophenol (ex Aldrich) (50g 0.35mol) was dissolved in 2.5 M hydrochloric acid (500ml), cooled to 0 °C and a solution of sodium nitrite (25.3g, 0.37mol) in water (50 ml) was slowly added over 20 minutes at 0-5 °C, stirred for 30 minutes, then a solution of potassium iodide (70g, 0.42 mol.) in water (100ml) was added slowly at 0 °C. The reaction mixture was then allowed to warm to 10 °C over 3 hours. The product was then extracted with ethyl acetate (200ml), washed with 10% sodium bisulphite, water, and was dried over magnesium sulphate and evaporated down to dryness. The product was purified by column chromatography with 5% ethylacetate in hexane to give an orange solid. wt.62g. 70% yield.

b) Intermediate II: 2-Benzyloxy-5-chloro-iodobenzene.

4-Chloro-2-iodophenol (57g. 0.22M was dissolved in acetonitrile (500mls), ceasium carbonate (72.6g, 0.22M.) was added slowly giving rise to an exotherm (19-24° C) over 30 minutes. The reaction mixture was then kept at 24°C for a further 5 hours. The reaction mixture was then stirred at 40 °C for 4 hours, then stirred at room temperature over night. The reaction mixture was filtered and evaporated down to a pink/brown solid. After trituration with water (200ml) the suspension was filtered and recrystallised from hexane (200ml) giving the title compound 50.2g, 65% yield. A second crop gave a further 22.7g. Total yield after drying 88%.

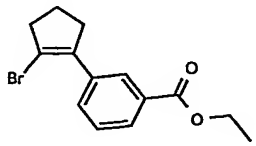
Rt=13.20 min

c) Intermediate III: (2-Benzyloxy-5-chlorophenyl)-boronic acid (WO 01/19814 A2)



2-Benzyloxy-5-chlorophenyl iodide (5g 0.0145 mol) in diethyl ether/tetrahydrofuran (50:50) was cooled to –100°C. n-Butyl lithium, 1.6M solution in hexanes (10mL, 0.016 mol) was added dropwise over 15min under nitrogen. The reaction mixture was then allowed to rise to –70°C for 1h. Triethylborate (9mL, 0.03 mol) was added dropwise under nitrogen. The cooling bath was then removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then quenched with 2N hydrochloric acid (40mL) and stirred vigorously at room temperature for 1h. The product was then extracted with ethyl acetate, dried over magnesium sulphate and evaporated down to an oil. Purification was carried out on a Biotage (90g cartridge) with ether / iso-hexane (50:50) to give the required product (wt; 2.8g i.e. 74% yield)

d) Intermediate IV: 3-(2-Bromocyclopent-1-enyl)-benzoic acid ethyl ester

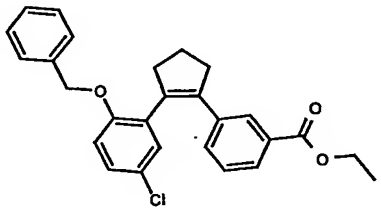


1,2-Dibromocyclopentene (Ex ALDRICH 27,732-0) (5g, 0.0221 mol), (3-ethoxycarbonylphenyl) boronic acid (Ex Combiblocks inc. BB-2117-005) (4.26g, 0.0221 mol), $Pd(0)[PPh_3]_4$ (0.5g) and

potassium carbonate (5g) were stirred at 80°C under nitrogen for 18h in dimethoxyethane (30mL). The reaction mixture was then filtered through Kieselguhr and evaporated down to an oil. Purification was carried out on a Biotage (90g column) using iso-hexane containing a gradient of dichloromethane (0-30%) to give the required product (wt: 1.15g i.e. 30% yield)

^{1}H NMR (400MHz, $CDCl_3$) 1.40 (3H, t, J=7Hz), 2.00-2.12 (2H, m), 2.75-2.94 (4H, m's), 4.39 (2H, q, J=7Hz), 7.43 (1H, t, J=8Hz), 7.85 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.22 (1H, s).
LC/MS rt 3.82, [MH+] 295, 297

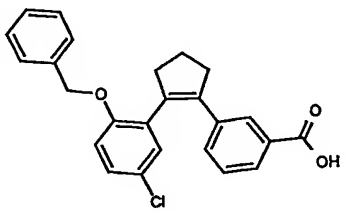
e) Intermediate V 3-[2-(2-Benzyloxy-5-chlorophenyl)-cyclopent-1-enyl]-benzoic acid ethyl ester



3-(2-Bromocyclopent-1-enyl)-benzoic acid ethyl ester (0.148g, 0.0005 mol), Pd(0)[PPh_3]$_4$ (30mg), potassium carbonate (0.2g) and (2-benzyloxy-5-chlorophenyl) boronic acid (150mg, 0.0005 mol) in dimethoxyethane (5mL) were refluxed for 17h under nitrogen. The reaction mixture was then filtered through Kieselghur and evaporated down to an oil.
Purification was carried out on a Water's separation pack (10g) with dichloromethane/iso-hexane giving the product (85mg).

^{1}H NMR (400MHz, $CDCl_3$) 1.31 (3H, t, J=7Hz), 2.01-2.12 (2H, m), 2.81-2.88 (4H, m's), 4.28 (2H, q, J=8Hz), 4.93 (2H, s), 6.81 (1H, d, J=8Hz), 7.02, (1H, d, J=2Hz), 7.10-7.33 (8H, m's excess), 7.76-7.86 (2H, m).
LC/MS , rt 4.21, [MH+] 433.

f) 3-[2-(2-Benzyloxy-5-chlorophenyl)-cyclopent-1-enyl]-benzoic acid



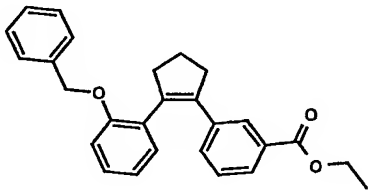
3-[2-(2-Benzyloxy-5-chlorophenyl)-cyclopent-1-enyl]-benzoic acid ethyl ester (80mg) was refluxed for 1h in methanol/2N sodium hydroxide (10:10mL). The reaction mixture was then evaporated

down to 3mL. 2N Hydrochloric acid (10mL) was added and the product extracted with dichloromethane (2x 10mL), dried over magnesium sulphate and evaporated down to an oil which solidified on standing (wt: 70mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.00-2.18 (2H, m), 2.80-3.50 (4H, m's), 4.94 (2H, s), 6.82 (1H. d J=9Hz), 7.02 (1H, d, J=2Hz), 7.10-7.40 (8H, m's excess), 7.86 (1H, d, J=7Hz), 7.90 (1H, s).
LC/MS RT = 3.63min [MH-] 403, 404.

Example 2 3-[2-(2-Benzyloxy-phenyl)-cyclopent-1-enyl]-benzoic acid

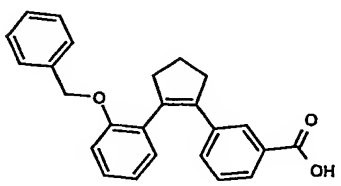
g) Intermediate I: 3-[2-(2-Benzyloxy-phenyl)-cyclopent-1-enyl]-benzoic acid ethyl ester



3-(2-Bromo-cyclopent-1-enyl)-benzoic acid ethyl ester (Intermediate IV of Example 1) (0.148mg, 0.0005mol), tetrakis-triphenylphosphine palladium (30mg), potassium carbonate (200mg) and (2-benzyloxyphenyl) boronic acid (110mg, 0.0005mol) in dimethoxyethane (5mL) were refluxed for 17h under nitrogen. The reaction mixture was then filtered through Keiselghur and evaporated down to an oil. Purification was carried out on a Water's separation pack (10g) cartridge with dichloromethane/iso hexane giving the product (120mg).

^{1}H NMR (400MHz, $CDCl_3$) 1.30 (3H, t, J=7Hz), 2.01-2.13 (2H, m), 2.84-2.99 (4H, m's), 4.27 (2H, q, J=7Hz), 5.00 (2H, s), 6.85 (1H, td, J=1Hz, J=7Hz), 6.92 (1H, d, J=8Hz), 7.02 (1H, d, J=7Hz), 7.11-7.34 (8H, m's excess), 7.76 (1H, d, J=8Hz), 7.85 (1H, s).
LC/MS RT = 4.09min

h) 3-[2-(2-Benzyloxy-phenyl)-cyclopent-1-enyl]-benzoic acid



3-[2-(2-Benzyloxyphenyl)-cyclopent-1-enyl] benzoic acid ethyl ester (120mg) was refluxed for 1h in methanol/2N sodium hydroxide (10/10mL). The reaction mixture was then evaporated down to 3mL on the Buchi. 2N Hydrochloric acid was added. The product was extracted with dichloromethane (2x 10mL), dried over magnesium sulphate and evaporated down to an oil which solidified on standing (wt: 100mg).

^{1}H NMR (400MHz, $CDCl_3$) 2.01-2.13 (2H, m), 2.85-3.00 (4H, m's), 5.00 (2H, s), 6.86 (1H, t, J=7Hz), 6.92 (1H, d, J=8Hz), 7.02 (1H, dd, J=2Hz, J=7Hz), 7.12-7.35 (8H, m's excess), 7.82 (1H, d, J=8Hz), 7.91 (1H, s).

LC/MS : RT = 3.81min [MH+] 371, [MH-] 369

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity *in vitro* and *in vivo* and their selectivity. The prostaglandin receptors investigated are DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

The ability of compounds to antagonise EP_1 & EP_3 receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of EP_1 or EP_3 receptors by the natural agonist hormone prostaglandin E_2 (PGE_2). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE_2 can mobilise. The net effect is to displace the PGE_2 concentration-effect curve to higher concentrations of PGE_2. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP_1 or EP_3 calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP_1 or EP_3 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10μg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE_2 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE_2 (pIC_{50}) may then be estimated.

By application of this technique, compounds of the examples had an antagonist pIC_{50} value of about 7.6 at EP_1 receptors and pIC50 value of < 6.0 at EP_3 receptors.

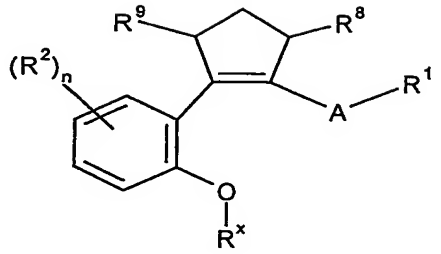
No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be

directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

Claims

1. A compound of formula (I);



(I)

wherein;

A represents an optionally substituted phenyl, or a 5- or 6- membered heterocyclyl group;

R^1 represents CO_2R^4, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted (C_{1-6})alkyl, optionally substituted (C_{1-6})alkenyl, $-SO_2(C_{1-6})$alkyl, $-SO_2NR^5R^6$, $-NR^5CONR^5R^6$, tetrazolyl or $COSO_2NR^5R^6$;

R^2 independently represents halo, optionally substituted (C_{1-6})alkyl, CN, SO_2R^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted (C_{1-8})alkyl or $-CH_2$-phenyl;

R^4 represents H or an optionally substituted (C_{1-6})alkyl;

R^5 represents H or an optionally substituted (C_{1-6})alkyl;

R^6 represents H or an optionally substituted (C_{1-6})alkyl, optionally substituted $-SO_2$aryl, optionally substituted $-SO_2$heterocyclyl group, CN or COR^7;

R^7 represents H or an optionally substituted aryl;

R^8 and R^9 independently represent H or (C_{1-6})alkyl;

n is an integer from 0 to 2;

m is an integer from 0 to 2;

wherein R^1 is attached to the group A in the 3 position relative to the bond attaching A to the cyclopentene ring;

or a pharmaceutically acceptable derivative thereof.